Original Article

A Novel Combined Index of D-Dimer, Fibrinogen, Albumin, and Platelet (FDAPR) as Mortality Predictor of COVID-19

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ABSTRACT

Background: In coronavirus disease 2019 (COVID-19) caused by SARSCoV2 viruses, coagulation abnormalities are strongly correlated between disease severity and mortality risk. **Aims:** The aim was to search for new indices to determine mortality risk. Fibrinogen times D-dimer to albumin times platelet ratio calculated with the formula (FDAPR index: ((Fibrinogen × D-dimer)/(Albumin × Platelet)) investigated as a mortality marker in COVID-19 patients. The hospitalization data of 1124 patients were analyzed from the electronic archive system. Hemogram, coagulation, and inflammatory markers were investigated in the study group. **Materials and Methods:** All statistical analyses like the student t-test, Mann–Whitney U, Kaplan–Meier, and Cox hazard ratio, were performed with the SPSS 22.0 program. **Results:** Prothrombin time was prolonged significantly in patients ($P < 0.05$) compared to healthy subjects (n = 30). D-dimer and fibrinogen were high, and albumin and platelet counts were low in COVID-19 patients (all, $P < 0.001$). When the data of 224 non-survivors and 900 survived patients were compared, D-dimer and fibrinogen were higher, and albumin and platelet lower (all, $P < 0.001$) compared to mild and severe patients. At the cut-off value of 0.49, the FDAPR index was performed with 89.1% sensitivity and 88.6% specificity. FDAPR index had the highest mortality predictive power ($P < 0.01$; HR = 5.366; 95% CI; 1.729–16.654). **Conclusions:** This study revealed that the FDAPR index could be used as a mortality marker of COVID-19 disease.

KEYWORDS: *Biomarker, coagulation, D-dimer, mortality, SARS-CoV2*

INTRODUCTION

In the global outbreak of the new coronavirus disease 2019 (COVID-19), 20% of all patients were severely and critically ill[1] and the mortality rate of critically ill patients reached 49%.[2] Among the various clinical consequences of COVID-19 disease affecting all world health systems, those who developed coagulopathy showed the most critical clinical conditions and disproportionately poor outcomes.[3] Recently, the mortality rate of disseminated intravascular coagulation caused by COVID-19 has been reported to be 71.4%.[4] It has been reported that the common coagulation dysfunction is associated with the severity of COVID-19 and can endanger patients' lives.[5]

Hospitalized, critically ill patients with COVID-19 demonstrated that they often have a high prevalence of laboratory abnormalities consistent with hypercoagulability and clinically high thromboembolic events.[3]

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In viral infections, the coagulation cascade is activated as a host defense to limit the spread of pathogens.[6] Primarily, there is an adaptive hemostasis response associated with a systemic inflammatory response. As a result of the increased inflammatory activity, fibrinogen levels increase significantly and thrombin is formed.[7] Additionally, procoagulant reactions are induced by increased cytokine production during virus infection and increased expression of tissue factor that initiates activation in coagulation. However, other factors in the cell membrane such as phosphatidylserine, neutrophil extracellular traps, and damage-related molecular patterns may also play a role in COVID-19.[8]

It is important to examine procoagulant changes in COVID-19 in terms of coagulation/fibrinolysis and platelet dysfunction and endothelial dysfunction.[9] However, routine tests such as Prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, and fibrinogen used as coagulation markers have some limitations such as using different units and the effects of anticoagulation treatment.[10]

The purpose of the study was to retrospectively examine the changes in coagulation tests in patients with COVID-19 at hospitalization and the success of overcoming the uncertainties and controversies/deficiencies in the use of tests alone with fibrinogen to albumin ratio (FAR) and Fibrinogen times D-dimer to albumin times platelet ratio (FDAPR) indices using combined parameters.

Subjects and Methods

This retrospective cohort study was carried out at Research Hospital between March 11, 2020, and March 01, 2021, in accordance with the MoH Diagnosis and Treatment Guidelines[11] after approval of the non-interventional clinical researches Ethics Committee on June, 18.2020.167.06.30.

Patients with COVID-19 positive for real-time q-polymerase chain reaction (RT-qPCR) of nasopharyngeal samples (n = 1124) were included in the study. Additionally, healthy participants with COVID-19 negative RT-PCR of nasopharyngeal samples (n = 30) were evaluated as the control group.

Demographic information, epidemiological history, clinical symptoms, comorbidities, imaging features, laboratory data, and length of hospitalization were collected through an electronic medical record system. Complete blood count data were analyzed using the ABX Pentra DX 120 (Horiba Medical, Montpellier, France) hematology analyzer. Biochemical tests were performed with the Roche's Cobas 8000 c502 Analyzer (Roche diagnostics; Geneva, Switzerland). Coagulation tests were performed with the Sysmex CS-2500 System coagulation analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany).

The D-dimer results were expressed as μg/mL fibrinogen equivalent unit (FEU). The laboratory reference range for D-dimer was 0 to 0.5 mg/L FEU. All measurements were performed within 2 h after blood sampling.

COVID-19 PCR test

RT-qPCR tests (Bioeksen, R&D Technologies Ltd., Istanbul, Turkey) were performed in the medical microbiology laboratory from oropharyngeal and nasopharyngeal swab samples of patients with suspicion of COVID-19 infection. The swab samples collected were taken into tubes containing 2 to 3 ml vNAT™ buffer. Viral RNAs were extracted in vNAT™ buffer without subjecting to an extraction process.

Diagnosis and follow-up

COVID-19 was diagnosed according to Diagnosis and Treatment Guidelines.[11] Patients with acute respiratory tract infection developed in the last 14 days, required hospitalization due to fever, cough, dyspnea, tachypnea, hypoxemia, hypotension, had diffuse radiological findings on lung imaging, change in consciousness, and were found to be SARS-CoV-2 positive by molecular methods were considered to have COVID-19.

In this study, we classified COVID-19 patients into three groups based on the severity of their illness (mild, severe, and critical). Patients were assigned to these groups based on their length of hospitalization, symptoms, accompanying diseases, radiological findings, and treatments. Mild patients had mild or no signs of pneumonia. Patients with dyspnea, hypoxia, or opacities over 50% in lung imaging within 24 to 48 h of hospitalization in the severe group. Other patients with respiratory failure, shock, or multiple organ failure in the critical group were investigated in this study.[1] Patients' survivals were evaluated further.

Statistical evaluation

We report the frequency and percentage values for categorical variables and mean ± standard deviation and minimum-maximum values for continuous variables.

Parametric/non-parametric distribution was determined by performing the Kolmogorov–Smirnov test for all groups. The student's t-test was used for variables with parametric distribution and the Mann–Whitney U test for variables with non-parametric distribution. A cut-off level for biomarkers was determined using the receiver operator characteristics (ROC) curve and the median value.

Results were compared by Kaplan–Meier survival analysis. Hazard ratio (HR) and 95% confidential interval (95% CI) were calculated by log-rank tests. The prognostic values of the indices and clinical variables were analyzed with Cox-proportional hazard models. The *P* values less than < 0.05 were considered statistically significant. All statistical analyses were conducted with the SPSS 22.0 program (SPSS Inc., Chicago, IL).

Results

All participants were examined in Table 1. Platelets decreased significantly in the COVID-19 patients than in healthy participants ($P < 0.001$). Although PT ($P < 0.01$) was prolonged significantly, slightly prolonged in APTT was observed with no significant difference ($P > 0.05$). In addition, there was a significant difference in fibrinogen, D-dimer, c-reactive protein (CRP), and albumin levels compared to the control group ($P < 0.01$) [Table 1].

As seen in Table 2, COVID-19 patients have been hospitalized for 8.82 (2-24) days. In computerized tomography (CT) findings, local opacities were more at 42.9%. Fever and cough were the most observed symptoms (46.6% and 57.1% respectively). Hypertension was the most observed comorbidity (23.2%) [Table 2].

Differences between survivors and non-survivors of COVID-19 patients are presented in Table 3; coagulation

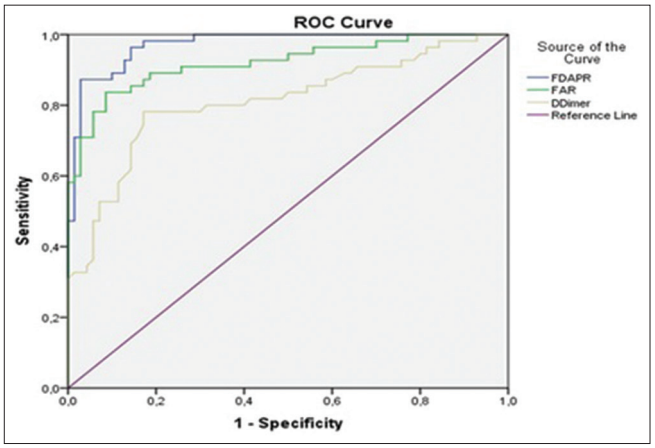

Figure 1: ROC curve for distinguishing survivors and non-survivors of COVID-19 patients.

Table 1: Characteristics of study participants

	PCR (-) Healthy (*n*: 30)	PCR (+) All Patients (*n*: 1124)	*P*
Gender (Female/Male)	9 (30%)/21 (70%)	472 (57%)/642 (43%)	
Age (years)	44.30±9.48	55.97±19.94	0,000
C-reactive protein (mg/dL)	0.20 (0.18-0.22)	75.91 (44.1-102.2)	0,000
APTT (sn)	23.44±1.62	24.73±2.80	0,283
PT (sn)	12.30±0.66	13.24±2.11	0,007
D-dimer (mg/L FEU)	0.20 (0.18-0.22)	1.27 (0.17-2.27)	0,000
Fibrinogen (mg/dL)	226.97±40.72	321.23±60.21	0,000
Platelet (*10^6/L)	255.40±35.50	197.46±89.02	0,000
Albumin (g/dL)	4.72±0.33	3.64±0.62	0,000
FAR	48.42±9.58	92.26±29.08	0,000
FDAPR	0.04±0.01	0.93±0.13	0,000

APTT: activated partial thromboplastin time, PT: prothrombin time, FAR: fibrinogen to albumin ratio, FDAPR: (fibrinogen×D-dimer) to (albumin×platelet) ratio

Table 2: Clinical data of COVID-19 patients

	COVID-19 cases (*n*=1124) %				
Hospitalized Time	8.82 (2-33) (day)				
CT results		**Comorbidity**		**Symptoms**	
No findings	261 (23.2%)	Hypertension	261 (23.2%)	Fever(>38.2^{0}C)	524 (46.6%)
Local opacities	482 (42.9%)	Diabetes Mellitus	181 (16.1%)	Cough	642 (57.1%)
Diffuse opacities	381 (33.9%)	Cancer	80 (7.1%)	Shortness of breath	261 (23.2%)
		Others	261 (23.2%)	Headache	141 (12.5%)
		No comorbidity	341 (30.3%)	Throat ache	181 (16.1%)
				Myalgia	100 (14.3%)
				Loss of sensation (anosmia. etc.)	100 (8.9%)
				Vomiting	40 (3.6%)
				Diarrhea	80 (7.1%)

CT: computerized tomography

tests measured at the time of admission to the hospital were significantly higher in D-dimer, fibrinogen, platelet, FAR, and FDAPR and significantly lower in albumin in non-survivors than survivors (all, $P < 0.001$) [Table 3].

In the ROC analysis applied; area under curve (AUC) values for D-dimer, FAR, and FDAPR parameters were significant diagnostic adequacy in determining mortality risk (0.811, 0.921, and 0.972, respectively) [Table 4, Figure 1]. The sensitivity and the specificity for D-dimer at 1.05 mg/L FEU cut-off value were 78.0% and 80.0%, respectively. For the specificity of FAR, the cut-off value at 90.14 was 85.5% and the sensitivity was 85.7%. For FDAPR, the sensitivity of the 0.49 cut-off value was 89.1% and the specificity was 88.6%.

Kaplan–Meier and Cox proportional hazard analyses were performed for survival. FDAPR was a significant predictor of mortality above (>0.49) the optimal cut-off value ($P < 0.001$) [Figure 2]. Then, the HR for FAR ($P < 0.01$, HR = 3.183 95% CI: 1.417-7.146) was found 3.183. D-dimer relation with survival was not significant ($P > 0.05$ HR = 1.143 95% CI: 0.541-2.411). The mortality estimation of FDAPR at the cut-off value of 0.49 was the strongest ($P < 0.01$; HR = 5.366 95% CI; 1.729-16.654) [Figure 2] [Table 5].

Table 3: Differences between survivors and non-survivors of COVID-19 patients

	Survivors (*n*: 900)	Non-survivors (*n*: 224)	*P*
Age (years)	**45,88±17,60**	65,51±17,24	0,000
Hospitalization days	8,36±4,929	9,63±4,85	0,114
D-dimer (mg/L FEU)	0,80±0,45	1,91±1,28	0,000
Fibrinogen (mg/dL)	304,54±47,22	356,10±64,63	0,000
Platelet (*10^6/L)	258,69±71,026	131,89±40,77	0,000
Albumin (g/dL)	4,09±0,30	3,06±0,43	0,000
FAR	74,01±15,60	116,47±26,95	0,000
FDAPR	0,27±0,19	1,73±1,27	0,000

APTT: activated partial thromboplastin time, PT: prothrombin time, FAR: fibrinogen to albumin ratio, FDAPR: (fibrinogen×D-dimer) to (albumin×platelet) ratio

Discussion

In our study, PT, D-dimer, and fibrinogen levels were significantly higher in the COVID-19 patients compared to healthy subjects, and the platelet count and albumin levels were significantly lower [Table 1]. Similar changes were observed in the same parameters of non-survivors compared with the survivors [Table 2].

Generally, these parameters were at normal values in the early stages of patients with asymptomatic disease and those with mild diseases.[12] Abnormally high D-dimer values were seen in 43% of non-severe patients, 60% of critically ill patients, and 45% of all cases.[1] **Srivastava *et al*.**[13] reported decreased levels of fibrinogen in people

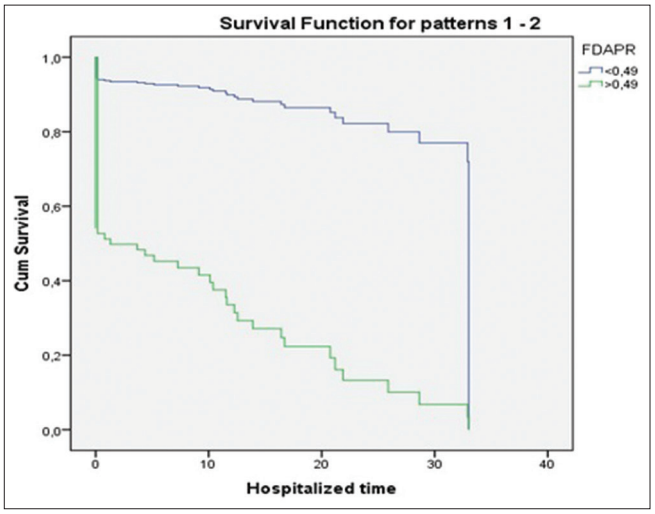

Figure 2: FDAPR group effect in cox analysis for survival.

Table 4: Analysis of variables in COVID-19 patients with ROC curve

Test Variable (s)	Cut-off	Area under curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval		Specificity (%)	Sensitivity (%)
					Lower Bound	Upper Bound		
D-Dimer (mg/L FEU)	1,05	0,811	0,041	0,000	0,731	0,891	80,0	78
FAR	90,14	0,921	0,026	0,000	0,870	0,971	85,5	85,7
FDAPR	0,49	0,972	0,012	0,000	0,948	0,996	89,1	88,6

FAR: fibrinogen to albumin ratio, FDAPR: (fibrinogen×d-dimer) to (albumin×platelet) ratio, Sig: significance.

Table 5: Variables in the equation of cox analysis

	B	SE	Wald	df	*P*	HR: Exp (B)	95,0% CI for Exp (B)	
							Lower	Upper
D-dimer group	0,133	0,381	0,122	1	0,726	1,143	0,541	2,411
FAR group	1,158	0,413	7,870	1	0,005	3,183	1,417	7,146
FDAPR group	1,680	0,578	8,454	1	0,004	5,366	1,729	16,654

HR: hazard ratio

who died in their study, although higher fibrinogen values[1] have been reported in the COVID-19 patients in other studies. In the light of these evaluations, it is obvious that coagulation abnormalities are a common condition in COVID-19 disease. However, changes in coagulation tests such as D-dimer,[1] PT,[14] platelet[15] fibrinogen,[1] and albumin[15] as a result of hyper-inflammation and coagulopathy have been shown as potential prognostic markers for severe/critical illness and/or mortality in COVID-19. However, it has been reported that they have various limitations in their use as markers alone.[16]

Determining high-risk patients or mortality risk in COVID-19 disease is very important for treatment planning. In the ROC analysis examined in our study, the AUC value for D-dimer was 81% and the sensitivity was 80.0% and the specificity was 78% in the cut-off 1.05. Similar to our findings, **Zhou *et al.*[2]** reported that an increased mortality rate was an independent indicator when D-dimer levels were above >1 mg/L. However, guidelines suggest different values for D-dimer above 2 mg/L[17] or 2- to 4-fold or 6-fold increase.[18] D-dimer levels at hospitalization have been reported to be a mortality marker with a sensitivity of 92% and a specificity of 83% above as high as 2 µg/ml (4-fold).[19] It was necessary to follow-up on the values, as accurate prognosis evaluation cannot be made with only hospital admission data.[20] For this reason, a test alone is not sufficient to predict the severity of COVID-19 disease in predicting mortality.[16] In our study, although the AUC of D-dimer (1.05 mg/L FEU) as a mortality marker above the optimal cut-off value was 81%, it was not found significant in the Cox hazard analysis assessment ($P > 0.05$). Therefore, the D-dimer test alone does not appear to be sufficient for clinical decisions.

In COVID-19, the prothrombotic effect of hypoalbuminemia was associated with an increased risk of arterial and venous thrombosis. Serum albumin concentrations were significantly lower in COVID-19 patients with increasing disease severity or death.[21] It was known that formulas that use coagulopathy parameters together with albumin may reflect inflammation more effectively.[22] Of these formulas, FAR was used as an effective marker of inflammation and is elevated in severe infections.[15] **Bi *et al.*[15]** revealed that the FAR index in severe COVID19 patients was associated with disease severity and was a strong negative predictor of disease progression at a cut-off value of 0.0883 ((0.9474, (95% CI: 0.845-0.986)). FAR, a combined marker, may be a stronger marker than D-dimer, which is considered the best marker for mortality risk in studies conducted so far. Nevertheless, a formula without D-dimer in indices to be used such as FAR may be insufficient to effectively reflect the clinical situation. To our knowledge, this present study was the first concerning FDAPR index.

In particular, a formula involving the combined use of parameters (D-dimer, fibrinogen, PLT, and albumin) associated with increased risk of COVID-19 disease may offer more valuable results. In fact, in our study, the FDAPR index was significantly higher in the patient group compared to the healthy controls and in non-survivor patients compared to the survivors (both, $P < 0.01$). The AUC value (0.972) in the analyzed ROC curve showed that FDAPR could be used as an important mortality marker at the optimal cut-off value of 0.49 ($P = 0.004$). It was obvious that FDAPR was a better indicator than FAR and D-dimer in predicting the mortality risk. Such an index has never been used in the literature. At the same time, strong mortality estimation could be predicted according to the FDAPR index ($P < 0.01$), but not according to FAR and D-dimer in survival analysis ($P > 0.05$, $P < 0,01$, respectively).

Limitations

Our study should be interpreted with some limitations. The first was its retrospective nature. Second, the effects and intensities of antithrombotic/anticoagulant treatments on the predictive value of D-dimer could not be investigated. Third, because these markers have differences such as race or age, study findings may not apply to other regions and races.[23,24] Therefore, our findings should be supported by large-scale, multicentered, randomized studies.

Conclusion

Coagulation parameters (PT, D-dimer, and fibrinogen) were increased significantly in COVID-19 patients. The mortality predictive powers of the D-dimer, FAR, and FDAPR index were higher ($P < 0.01$, $P > 0.05$, $P < 0.01$, respectively). Compared to D-dimer and FAR, the mortality predictive value of the FDAPR index was higher and sensitivity was 89.1% and specificity was 88.6%. We propose that the FDAPR index, in which fibrinogen, D-dimer, platelet, and albumin among the coagulation system tests used in combination, could be used efficiently as a new predictive marker of mortality in COVID-19 patients.

FDAPR was the strongest predictor of COVID-19 mortality at admission to the hospital at a cut-off value of 0.49.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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